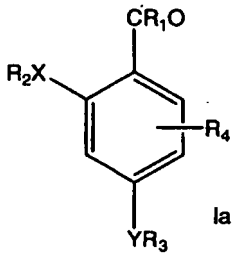
Amendments to the Claims

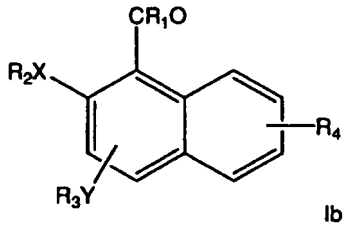
This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

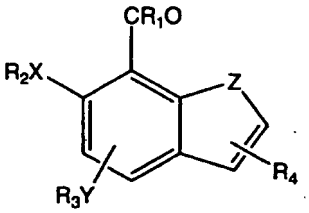
1. (Presently Amended) A positive charge-balanced linker according to general formulae (Ia to Ie):



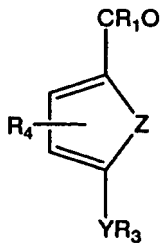
Ia



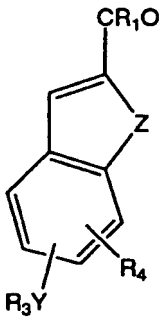
Ib



Ic



Id



Ie

General formulae (I)

wherein:

X = O or S;

Y is O, S or CH_2, CHR, CRR, where R is C_{1-7} alkyl;

Z is O or S;

R_1 is H or C_{1-7} alkyl;

R_2 is H or C_{1-7} alkyl;

R_4 is H or C_{1-7} alkyl at any vacant position on the aromatic ring;

R_3 is C_{1-7} alkyl-L_1-R_5-L_2- R_6-COOH, C_{3-10} cycloalkyl-L_1-R_5-L_2- R_6-COOH or Ar-C_{0-7} alkyl-L_1-R_5-L_2-R_6-COOH;

each of L_1 and L_2 is absent or ~~a suitable~~ is a linker ~~such as~~ selected from the group consisting of an amide CONH; ~~or~~ an ether -O-; ~~or~~ a thioether -S- ~~or~~; and a sulphone -SO_2-;

R_5 is C_{1-7} alkyl, C_{3-10} cycloalkyl or Ar-C_{0-7} alkyl each of which is substituted with either NR_8R_9, where the nitrogen atom is capable of being protonated in solution to give $N^+HR_8R_9$; or a quaternary nitrogen atom $N^+R_8R_9R_{10}$, such that R_5 contains a positive charge;

each of R_8, R_9 and R_{10} is independently C_{1-7} alkyl, C_{3-10} cycloalkyl or Ar-C_{0-7} alkyl, or any two or more of R_8, R_9 and R_{10} together form an alicyclic or arylalicyclic ring system;

R_6 is C_{1-7} alkyl, C_{3-10} cycloalkyl or Ar-C_{0-7} alkyl;

or a salt, hydrate, solvate, complex or prodrug thereof.

2.(original) compound as claimed in claim 1 wherein, independently or in any combination:

X is oxygen;

Y is oxygen;

R_1 is hydrogen, methyl or ethyl;

R_2 is hydrogen or C_{1-4} alkyl;

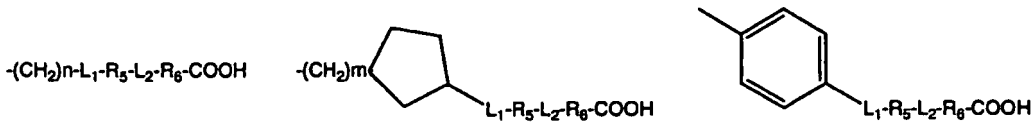
L_1 is an amide (CONH); and

L_2 is an amide (CONH).

3. (Presently Amended) A compound as claimed in claim ~~2~~ 1, wherein R_1 is hydrogen.

4. (Presently Amended) A compound as claimed in claim ~~2 or claim 3~~ 1, wherein R_2 is hydrogen or methyl.

5. (Presently Amended) A compound as claimed in ~~any one of claims 1 to 3~~ claim 1 wherein R_3 comprises



wherein n = 2-6; and

m = 1-3.

6. (Presently Amended) A compound as claimed in ~~any one of claims 1 to 5~~ claim 1, wherein ~~NHR_5CO (where the NH is part of the L_1 moiety and the CO is part of the L_2 moiety) the~~ L_1-R_5-L_2 is CO-NHR_5CO-NH and wherein NHR_5CO comprises a simple amino acid residue that contains a side-chain protonatable amine functionality.

7.(original) compound as claimed in claim 6 wherein NHR_5CO is represented by the formula:

$$-NH-CH[(CH_2)_pN^+R_8R_9R_{10}]CO-$$

wherein p is 1 to 5 and R_8, R_9 and R_{10} are as defined above.

8.(original) compound as claimed in claim 7, wherein p is 1 to 4.

9. (Presently Amended) A compound as claimed in ~~any one of claims~~ claim 1 ~~to 8~~ wherein R_8, R_9 and R_{10} ~~groups~~ are each independently C_{1-4} alkyl.

10. (Presently Amended) A compound as claimed in ~~any one of claims 1 to 8~~ claim 1 wherein L_2 is CONH; wherein R_6 is ~~combines with an NH group derived from the L_2 moiety and the terminal COOH to form an amino acid residue of the formula:~~

~~$-NH-(CH_2)_q-A_s-(CH_2)_rCOOH;$~~

$-(CH_2)_q-A_s-(CH_2)_r-$;

where q and r are each 0 to 3, provided that both q and r are not both 0;

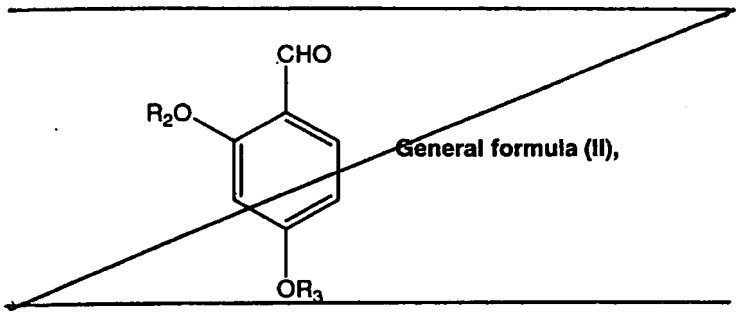
s is 0 or 1; and

A is a 5-10 membered stable monocyclic or bicyclic aromatic ring or a 3-6 membered carbocyclic or alicyclic ring.

11. (original) A compound as claimed in claim 10 wherein r and s are 0 and q is 1 or 2.

12. (Presently Amended) A compound ~~as claimed in any one of claims 1 to 11, which is a compound~~ of general formula (Ia) as defined in claim 1.

13. (Presently Amended) A compound as claimed in claim 12, ~~which is a compound of general formula (II):~~



General formula (II),

~~which is a compound of general formula (Ia) in which~~

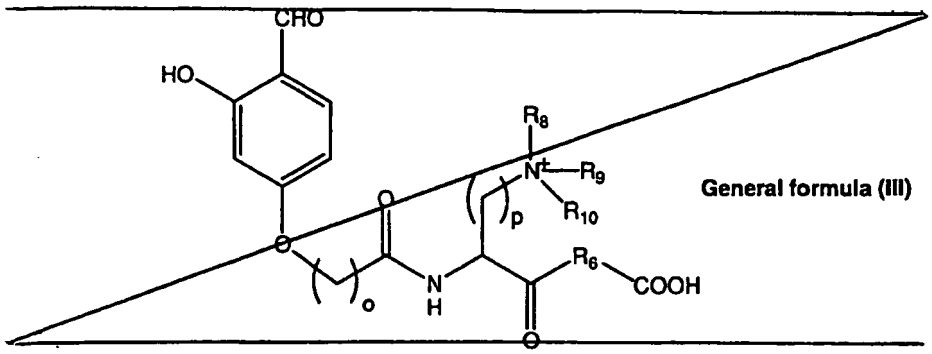
wherein

X and Y are O,

R_1 is H; and

R_2 and R_3 are as defined in claim 1.

14. (Presently Amended) A compound as claimed in claim 13, ~~which is a compound of general formula (III):~~



General formula (III)

wherein:

R_3 is $-(CH_2)_o$-C(O)-NH-CH(-$(CH_2)_p$-$N^+(R_8)(R_9)(R_{10})$)(-C(O)-R_6-COOH)

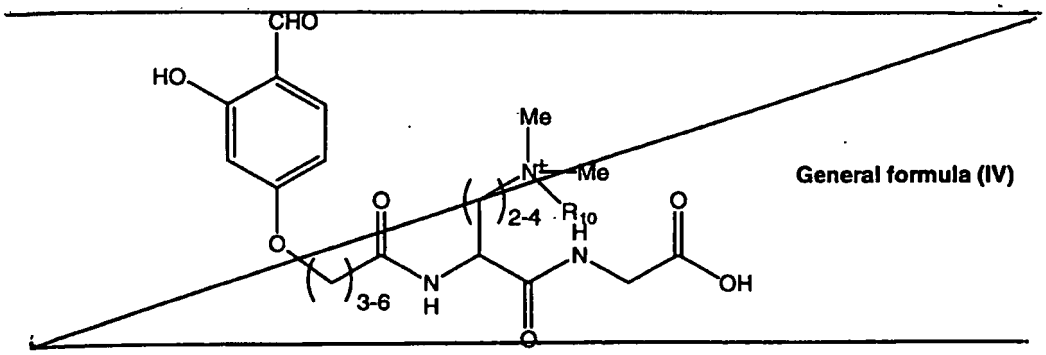
o is an integer from 2-6;

p is an integer from 1 to 5; and

R_6, R_8, R_9 and R_{10} are as defined in claim 1.

15. (original) A compound as claimed in claim 14, wherein p is an integer from 1 to 4.

16. (Presently Amended) A compound as claimed in claim 15, ~~which is a compound of general formula (IV):~~



General formula (IV)

wherein

R_3 is $-(CH_2)_o$-C(O)-NH-CH(-$(CH_2)_p$-$N^+(R_8)(R_9)(R_{10})$)(-C(O)-R_6-COOH)

o is an integer from 3 to 6;

p is an integer from 2 to 4;

R_8 and R_9 are methyl; and

R_{10} = H or methyl.

17. (Presently Amended) A process for the preparation of a compound of general formula (I) in which L_1 and L_2 are CONH, the process comprising:

(i) reacting a compound of general formula V:

$$H_2N\text{-}R_6\text{-}COOH \qquad (V)$$

wherein R_6 is as defined for general formula (I) in claim 1; and

wherein the compound of general formula (V) is bound at its C-terminus to a solid support;

with a compound of general formula (VI):

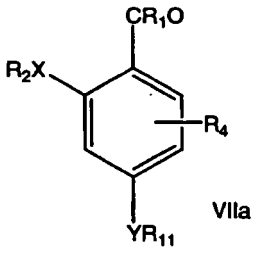
$$W\text{-}NH\text{-}R_5\text{-}COOH \qquad (VI)$$

wherein:

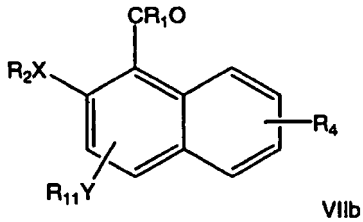
R_5 is as defined ~~for general formula (I)~~ in claim 1; and

W is a protecting group;

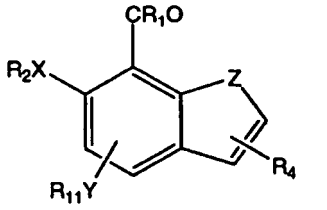
(ii) removal of the protecting group W and reaction with a compound of general formula (VII):



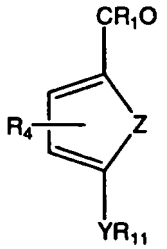
VIIa



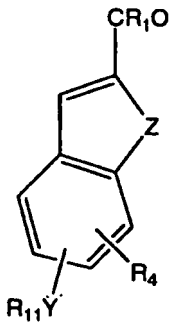
VIIb



VIIc



VIId



VIIe

General formulae (VII)

wherein

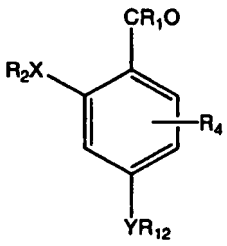
X, Y, Z, R_1, R_2, and R_4 are as defined ~~for general formula (I)~~ in claim 1; ~~and~~

R_{11} is C_{1-7} alkyl-COOH, C_{3-10} cycloalkyl-COOH or Ar-C_{0-7} alkyl-COOH; and

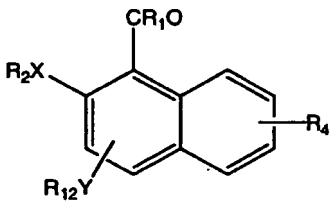
(iii) removal of the product from the solid support.

18. (original) A process as claimed in claim 17 wherein, in the compound of general formula (VI), W is a urethane protecting group.

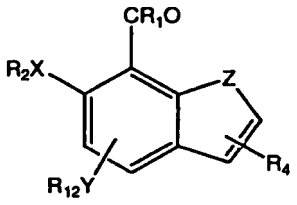
19. (Presently Amended) A compound of general formula (XIV):



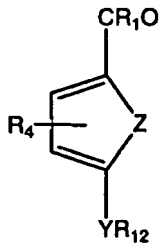
XIVa



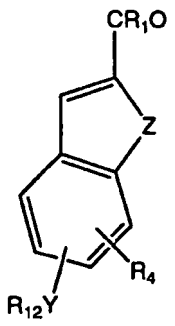
XIVb



XIVc



XIVd



XIVe

General formulae (XIV)

wherein

X, Y, Z, R_1, R_2, and R_4 are as defined ~~for general formula (I)~~ in claim 1; and

R_{12} is C_{1-7} alkyl-L_1-R_5-L_2-R_6CONHQ, C_{3-10} cycloalkyl-L_1-R_5-L_2-R_6CONHQ or Ar-C_{0-7} alkyl-L_1-R_5-L_2-R_6CONH-Q;

wherein L_1, L_2, R_5, and R_6 are as defined ~~in general formula (I)~~ in claim 1;

Q is a ~~residue which is~~ part of a carrier and Q ~~which either~~ contains ~~groups from which the~~ at least one amino group ~~"NH" moiety in R_{12} is derived or has been derivatised so as to include such groups~~; and

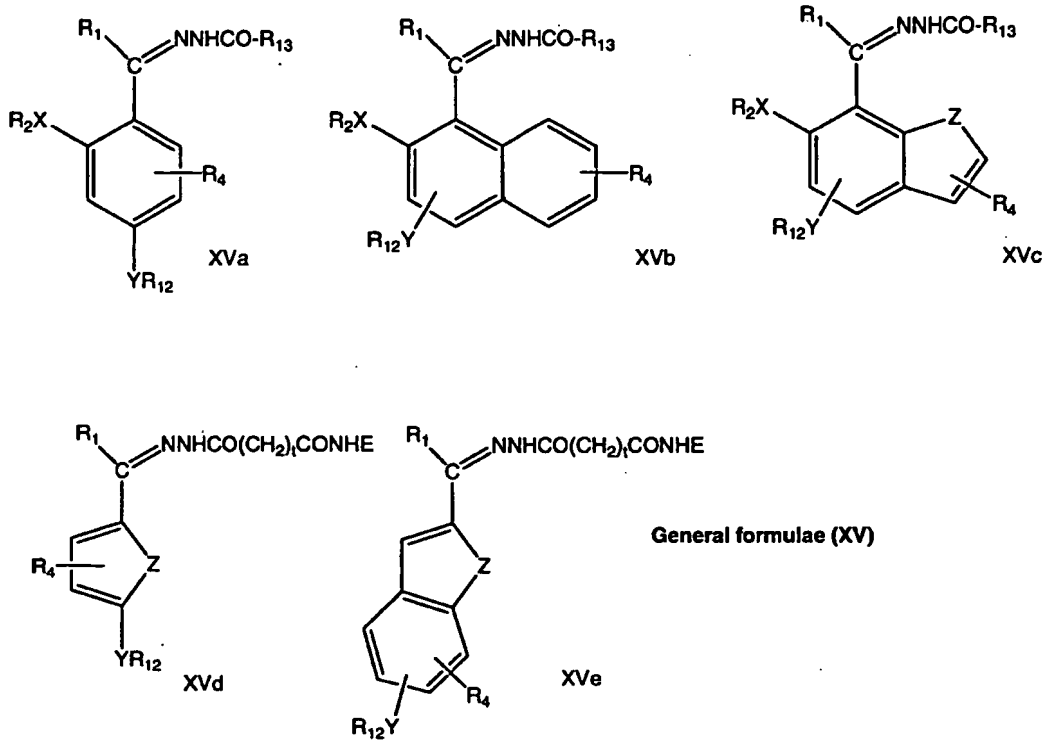
wherein the carrier may contain more than one Q ~~residues that already have 0,1,2,...*nn* linker molecules of general formula (I) attached;~~

~~wherein the integer *nn* is the total number of Q residues available for attachment of a linker molecule to a specific carrier, where *nn* will be different for each specific carrier~~.

20. (original) A compound as claimed in claim 19 wherein Q is part of a proteinaceous molecule, a polysaccharide, cellulose beads, a polymeric amino acid, a polymer, which may be a copolymer, an inactive virus particle or attenuated bacteria.

21. (Presently Amended) A process for the preparation of a compound as claimed in claim 19 ~~or claim 20~~, the process comprising reacting a compound of general formula (I) as defined above with a carrier.

22. (Presently Amended) A compound of general formula (XV):



wherein X, Y, Z, R_1, R_2, and R_4 are as defined ~~for general formula (I)~~ in claim 1;

R_{12} is as defined in ~~general formula (XIV) as claimed in~~ claim 19;

R_{13} is $(CH_2)_tCONH$-E, CONH-E, or G;

t is an integer from 1 to 5;

E is derived from an active moiety which either contains an amino group or has been ~~derivatised~~ derivatized to do so; and NHE is derived from the amino group of the active moiety;

G is an active moiety bound to the carbonylhydrazide through a carbon atom.

23. (original) A compound as claimed in claim 22 which comprises E or G groups derived from two or more active moieties.

24. (original) A process for the preparation of a compound of general formula (XV) as defined in claim 22, the process comprising reacting a compound of general formula (XIV) as defined above with a compound of general formula (XVIa), (XVIb) or (XVIc):

$E\text{-}NH\text{-}CO\text{-}(CH_2)_tCONHNH_2$	(XVIa)
$E\text{-}NH\text{-}CO\text{-}NHNH_2$	(XVIb)
$G\text{-}CO\text{-}NHNH_2$	(XVIc)

where E, G and t are as defined in claim 22.

25. (Presently Amended) A compound as claimed in claim 22 ~~or claim 23~~ which is soluble in aqueous solution.

26. (original) A compound as claimed in claim 25 wherein E or G is derived from an epitope or mimotope.

27. (Presently Amended) A compound as claimed in claim 26 wherein the epitope is a fragment~~, for example an antigenic determinant,~~ derived from a protein or peptide molecule or a variant thereof.

28. (Presently Amended) A compound as claimed in claim 26 ~~or claim 27~~ wherein the epitope is a B cell or T cell epitope.

29. (Presently Amended) A compound as claimed in ~~any one of claims~~ claim 25 ~~to 28~~ which includes another active moiety ~~selected from~~ comprising an immunomodulating compound ~~such as a lipid, adjuvant, an immunostimulating DNA sequence or cytokine~~ attached to the carrier protein.

30. (Presently Amended) A method for raising specific antibodies against ~~the~~ an epitope or mimotope, the method comprising ~~immunising~~ immunizing a subject with a compound as claimed in ~~any one of claims 26 to 29~~claim 26 comprising E or G derived from said epitope or mimotope.

31. (Cancelled)

32. (Cancelled)

33. (Cancelled)

34. (Presently Amended) A pharmaceutical composition comprising a compound as claimed in ~~any one of claims~~ claim 26 ~~to 29~~ together with a pharmaceutically acceptable excipient.

35. (Presently Amended) A ~~pharmaceutical~~ vaccine composition comprising a compound as claimed in claim ~~34 which is a vaccine composition and which further comprises a~~ 26 together with a pharmaceutically acceptable excipient and a pharmaceutically acceptable adjuvant.

36. (original) A non-destructive method of quantifying the extent and/or rate of reaction of a protein with a linker of general formula (I) as defined in claim 1 in which R_2 is H and X is O, the method comprising either:

a) measuring the intensity of the absorbance spectrum at a wavelength above 300nm and at a pH greater than 7 in order to detect the formation of a compound of general formula (XIV) in which R_2 is H and X is O; or

b) measuring the fluorescence emission upon excitation at a selected wavelength in order to detect the formation of a compound of general formula (XIV) as defined in claim 19 in which R_2 is H and X is O.

37. (original) A non-destructive method for quantifying the extent and/or rate of reaction of a linker-protein of general formula (XIV) as defined in claim 19 wherein R_2 is H and X is O, with an active moiety hydrazide, the process comprising measuring the intensity of the absorbance spectrum at a wavelength above 300nm and a pH less than 7.

38. (Presently Amended) A process for the preparation of a compound of general formula (XV) as defined in claim 22 in which:

R_2 is H and X is O;

the carrier has ~~multiple residues~~ more than one Q;

a first selected percentage of the Q ~~residues~~ groups is ~~derivatised~~ derivatized with a first active moiety; and, optionally

further selected percentages of the Q ~~residues~~ groups are ~~derivatised~~ derivatized with further active moieties;

the process comprising:

a) reacting a compound of general formula (XIV) as defined in claim 19 in which R_2 is H and X is O with a first compound of general formula (XVI) as defined in claim 24 at a pH less than 7;

b) monitoring the progress of the reaction by measuring the intensity of the absorbance spectrum at a wavelength of above 300nm and stopping the reaction when the intensity of the absorbance spectrum reaches the first selected percentage of the known maximum intensity; and optionally

c) reacting the product of steps (a) and (b) with one or more further compounds of general formula (XVI), monitoring the progess of the reaction by measuring the intensity of the absorbance spectrum at a wavelength of above 300nm and stopping the reaction when the intensity of the absorbance spectrum reaches further selected percentages of the known maximum intensity.

39. (original) A method for quantifying the extent and/or rate of release of an active moiety hydrazide from a compound of general formula (XV) as defined in claim 22 in which R_2 is H and X is O, the method comprising the measurement of the absorbance spectrum maximum at a wavelength above 300nm and at pH less than 7.

40. (Presently Amended) A compound as claimed in claim 22 ~~or claim 25~~ wherein E or G is a labelling moiety.

41. (Presently Amended) A compound as claimed in claim 22 ~~or claim 23~~ which is insoluble in aqueous solution.

42. (Presently Amended) A compound as claimed in claim 41 wherein E or G is a ligand which is specific for ~~an analyte or~~ a compound to be separated.

43. (original) A compound as claimed in claim 42 which contains additional E or G groups derived from labelling molecules.

44. (Presently Amended) A method of separating a compound from a mixture, the method comprising contacting the mixture with a compound of ~~general formula (XV) as defined in~~ claim ~~22~~ ~~in~~ 42 wherein ~~which~~ E or G is a ligand which ~~binds~~ is specifically ~~to the~~ for said compound ~~to be separated~~ and the carrier is a solid support.

45. (Presently Amended) An assay method comprising contacting a mixture suspected of containing an analyte with a compound of ~~general formula (XV) as described above~~ claim 55 in which E or G is a ligand ~~which binds specifically to the~~ for said analyte and the carrier is a solid support.

46. (Presently Amended) A wound dressing comprising a compound as claimed in claim 41 ~~wherein the carrier is a functionalised polymer of the type commonly used in wound dressings and E or G is a peptide growth factor, a chemo-attractant protein, a ligand or an analogue of one of these~~.

47. (Cancelled)

48. (Cancelled)

49. (Cancelled)

50. (original) A compound as claimed in claim 41 wherein the carrier is a polymer suitable for use in dialysis tubing and E or G is heparin for use in the preparation of dialysis tubing.

51. (New) Dialysis tubing comprising a compound as claimed in claim 50.

52. (New) A compound as claimed in claim 26 wherein the epitope is an antigenic determinant derived from a protein or peptide molecule.

53. (New) A compnd as claimed in claim 29 wherein the immunomodulating compound is a lipid, an adjuvant, an immunostimulating DNA sequence or cytokine.

54. (New) A compound as claimed in claim 25 where E or G is a labelling moiety.

55. (New) A compound as claimed in claim 41 wherein E or G is a ligand which is specific for an analyte.

56. (New) A compound as claimed in claim 41 wherein the carrier is a functionalized polymer of the type commonly used in wound dressings and E orG is a peptide growth factor, a chemo-attractant protein, a ligand or an analogue of one of these.